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Integration of recognition, diagnostic, and treatment strategies between prehospital emergency medical services and hospital emergency departments in the management of patients with acute sepsis and septic shock

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INTEGRATION OF RECOGNITION, DIAGNOSTIC, AND TREATMENT STRATEGIES BETWEEN PREHOSPITAL EMERGENCY MEDICAL SERVICES AND HOSPITAL EMERGENCY DEPARTMENTS IN THE MANAGEMENT OF PATIENTS WITH ACUTE SEPSIS AND SEPTIC SHOCK

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ABSTRACT

Sepsis and its manifestation as a shock state in “septic shock” have long caused medical issues and death worldwide. The disease requires quick identification, diagnosis, and intervention with very high mortality rates prevalent otherwise. Historically this has been due to limited awareness of the disease and misclassification of its prevalence, severity, and incidence. Luckily in the past decade there has been increased interest and therefore resources devoted towards improving care and further understanding a disease that is one of the leading causes of mortality in hospitals worldwide. Over the past handful of years novel interventions and diagnostic techniques have become available. Unfortunately, in many cases these new discoveries have not yet trickled down to many of the providers on the frontline and a large amount of variation in care exists across the country. Because of the time sensitivity of sepsis, it is imperative that individuals working in the areas of healthcare who first come in contact with these patients have a clear understanding of the newest advances and resources available. In this thesis the goal is to first analyze the current protocols and standards of care for sepsis and then secondly consider new developments available both in the hospital and in prehospital emergency

medical services (EMS). From the current information, strategies and protocols based on improvement of patient outcomes, can be streamlined and optimized moving forward. As predicted, there is currently an incredibly large amount of variation and knowledge on the subject with some areas implementing very progressive protocols while others still lack a sepsis protocol all together. In general, the current consensus in the field is that rapid identification and initiation of treatment is the most important component to long term survival. Improvement of outcomes therefore relies on standardization of protocols with incorporation of education components for healthcare providers. This aims to raise awareness and encourage utilization of the newest information and suggestions available. Increased interdisciplinary cooperation between prehospital providers in EMS and care providers in the hospital can also lead to improvement of recognition and treatment times for these patients. Future considerations were also examined that may potentially be applicable moving forward to improve these standards even further. There is a much opportunity available in each of these areas currently and progress is key to improving outcomes.

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ABBREVIATIONS

AEMT	Advanced Emergency Medical Technician
ALS	Advanced Life Support
ARDS	Acute Respiratory Distress Syndrome
BIPAP	Bi-level Positive Airway Pressure
BLS	Basic Life Support
BVM	Bag Valve Mask
CD4 B	Cluster of Differentiation 4 B Cell (immune system)
CD4 T	Cluster of Differentiation 4 T cell (immune system)
CDC	Center for Disease Control
CO2	Carbon Dioxide
CPAP	Continuous Positive Airway Pressure
CVA	Cerebrovascular Accident
CXCL-8	Interleukin-8
ED	Emergency Department
EGDT	End Goal Directed Therapy
EMR	Emergency Medical Responder
EMS	Emergency Medical Services

EMTB	Emergency Medical Technician Basic
EMTP	Emergency Medical Technician Paramedic
ETCO2	End-Tidal Carbon Dioxide
EUROBACT	European Society of Intensive Care Medicine
FiO2	Fraction of Inspired Oxygen
GCS	Glasgow Coma Scale
GI	Gastrointestinal
IBP	Invasive arterial blood pressure
ICU	Intensive care unit
IL	Interleukin
IM	Intramuscular
IN	Intranasal
IO	Intraosseous
IV	Intravenous
IVF	Intravenous Fluid
MAP	Mean Arterial Pressure
NiBP	Non-invasive Blood Pressure

NREMT	National Registry of Emergency Medical Technicians
PaO2	Partial Pressure of Oxygen
POC	Point of Care
qSOFA	Quick Sequential Organ Failure Assessment
SBP	Systolic Blood Pressure
SC	Subcutaneous
SIRS	Systemic Inflammatory Response System
SL	Sublingual
SOFA	Sequential Organ Failure Assessment
SpO2	Peripheral Capillary Oxygen Saturation
SSC	Surviving Sepsis Campaign
TF	Tissue Factor
TNF	Tumor Necrosis Factor
US	United States of America
UTI	Urinary Tract Infection
WHO	World Health Organization

INTRODUCTION

Sepsis and its associated disease processes, including severe sepsis, septicemia, and septic shock are currently recognized as one of the leading causes of death nationwide based on in-hospital mortality rates. A 2014 analysis of two patient groups, one from a northern California healthcare system, and another from a countrywide data set, estimates that anywhere between 34.7% to 55.9% of all inpatient hospital deaths occur with sepsis as a contributor.[1] Despite this high mortality rate sepsis has long been ill defined and poorly researched relative to other major medical conditions such as cancer and heart disease. This is partly due to low awareness as well as vague, inconsistent definitions of sepsis. This has started to improve only very recently and primarily just in the last decade. According to a survey done by the Sepsis Alliance, only 55% of all Americans had actually heard of sepsis in 2016.[2] More shockingly this number represents an increase of more than 25 million people when compared to a similar survey done in 2015. In addition to the lack of sepsis awareness the same survey found that only 28% could accurately identify symptoms of the condition.[2] These improving numbers are a promising step in the right direction but substantial work can still be done to increase awareness as well as improve current treatment strategies for the future. WHO recently adopted a resolution that encourages all member states to aim for "reduction of the burden of sepsis through improved prevention, diagnosis, and management" as there are many areas around the world where awareness and recognition rates are significantly less than the previously noted US statistics.[3] One of the most important aspects of treating sepsis and the focus of many campaigns worldwide has been the benefit of early recognition and the prompt initiation of treatment.[4] The majority of sick patients enter the hospital via the emergency department (ED) therefore it is the natural beginning of the screening process. The ED is also an opportunity for aggressive initial therapy options to be administered with the goal of decreasing mortality. One recent study showed that implementation of both a sepsis treatment algorithm as well as increased education of ED nurses led to both an increase in sepsis recognition of 21.5% as well as a decrease in patient mortality of 28%.[5] This then shows that reduction in recognition and treatment time in the ED can be a major factor in combating sepsis mortality. A promising possibility then arises when considering prehospital medicine, particularly emergency medical services (EMS), as a potential area to further improve these metrics. Current studies show that identification of patients with sepsis in the prehospital environment is somewhat poor and that improved education and implementation of screening tools may increase effectiveness of prehospital providers in accomplishing early diagnosis.[6] Efforts to integrate EMS detection and care with ED and definitive hospital interventions are more established and standardized in other time sensitive conditions such as acute myocardial infarction as well as cerebrovascular accident (CVA)/stroke and have shown to be effective in improving patient outcomes. [7,8] This thesis will attempt to examine the advances and information currently available regarding the treatment of sepsis in the pre-hospital setting and how it can be improved moving forward.

Definition:

In 2016 the Third International Consensus (Sepsis-3), a global task force of diversified medical professionals, established an updated definition of the terms "sepsis" and “septic shock”.[9] The goal of this effort was to describe the advances that have been made in recent years as the medical and scientific research community have increased their focus on the study of sepsis. [9] A simple search of the term “sepsis” in the PubMed Database shows an exponential increase in the number of articles which mention or include the word especially in the past twenty years (Figure 1). This represents the enormous growth in data and therefore understanding available today. Due to the rapid and still evolving state of sepsis care worldwide, the Sepsis-3 collaboration was focused on standardizing this information and terminology available today so that the field is on the same page moving forward.[9]

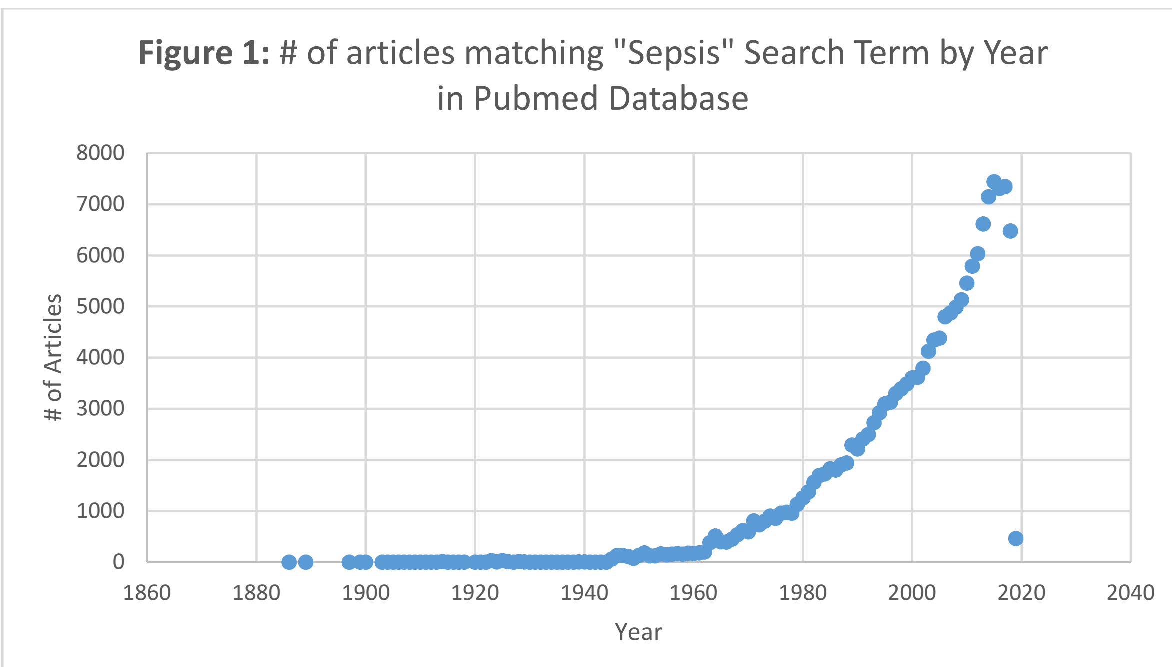

Figure 1: Number of Sepsis Publications Per Year *Taken from PubMed's "Results By Year" tool with Sepsis as the search term.* Data compiled from (https://www.ncbi.nlm.nih.gov/pubmed/?term=Sepsis, *February 21,2019*)

Prior to Sepsis-3, the definition of sepsis stemmed from the first international consensus which laid down the groundwork in 1991 (Sepsis-1).[9] These Sepsis-1 guidelines were based on the input of physicians worldwide and represented the first time sepsis had truly been categorized and consolidated into a standardized set of ideas and common terminology. The definition was expanded upon in 2001 by way of a task force with expanded diagnostic criteria (Sepsis-2) but the thinking had been mostly the same for more than 20 years.[9] The old definition was focused primarily on recognition through diagnostic measures that focused on the host's systemic inflammatory response (SIRS) to some sort of infection. Severe sepsis was defined in both Sepsis-1 and Sepsis-2 to be the point at which SIRS progressed to organ dysfunction.[9] Septic shock is specified once hypotension persists despite standardized fluid resuscitation measures. This definition was found to be largely limiting by the investigators of Sepsis-3 and inaccurate when used to identify sepsis patients. The definition had both poor sensitivity and specificity when it came to classifying patients with sepsis versus those with other medical conditions.[10,11] The new definition established by the members of Sepsis-3 defines sepsis as, "Life threatening organ dysfunction caused by a dysregulated host response to infection". Organ dysfunction is then further categorized based on the sequential (sepsis-related) organ failure assessment (SOFA) (Table 1). This score is mainly utilized in the intensive care unit (ICU) and ED settings to assess the severity of sepsis. Unfortunately, the SOFA score is not usable in EMS integration due to some of its parameters being unobtainable in the field.

Table 1: Sequential (Sepsis-Related) Organ Failure Assessment Score

	Score				
System	0	1	2	3	4
Respiration - PaO2/FiO2 mmHg (kPa)	≥400 (53.3)	≤400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation - Platelets, x $10^3/\mu L$	≥150	<150	<100	<50	<20
Liver - Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or dobutamine any dose	Dopamine 5.1-15 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
Central Nervous System - Glascow Coma Scale score	15	13-14	10-12	6-9	<6
Renal - Creatinine mg/dL (µmol/L) - Urine Output, mL/d	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500	>5.0 (440) <200

Catecholamine values are based on dosing of µg/kg/min in one-hour intervals. Glasgow Coma Scale (GCS) is a standard means of assessing neurological function and is on a 3-15 scale with a higher number representing more function. PaO2: *Partial Pressure of Oxygen*, FiO2: *Fraction of Inspired Oxygen*, MAP: *Mean Arterial Pressure*. Note In cardiovascular levels 2-4 MAP is no longer the parameter considered and it transitions to the level and type of vasopressor therapy administered. This is done because most patients scoring in the 2-4 range will require vasopressor therapy and then MAP cannot be considered as a true indicator of patient condition. This table was adapted from *The Third International Sepsis Campaign Paper (Sepsis-3)*[9]

In addition to encouraged utilization of the SOFA score, Sepsis-3 also developed the qSOFA score which is designed to be much simpler and easy to use upon initial patient contact. The qSOFA can be used on every patient with a simple assessment.

Those with qSOFA scores of 2 or greater with suspected infection and therefore potential sepsis will quickly get a more thorough examination[9]. As opposed to the SOFA score, qSOFA scores can easily be used in the prehospital setting.

Table 2: Breakdown of qSOFA score

qSOFA score	Assessment
1	Hypotension (SBP less than or equal to 100mmHg)
1	Tachypnea (greater than or equal to 22 breaths per minute)
1	Altered mental status (GCS less than or equal to 14)

If patient was found to have a qSOFA score of greater than 2 with suspected infection this indicates for potential sepsis and mandates further evaluation. Systolic Blood Pressure (SBP), Glasgow Coma Scale (GCS) is a standard means of assessing neurological function and is on a 3-15 scale with a higher number representing more function. Information taken from *The Third International Sepsis Campaign (Sepsis-3).*[9]

The consensus found that if a SOFA score is greater than or equal to 2 this corresponds to a mortality risk of approximately 10%. Therefore, a qSOFA score of 2 is an appropriate threshold to begin diagnosis and subsequent initiation of sepsis treatments.

Furthermore, in the new definition, septic shock represents a more serious progression of sepsis. Specifically, the distinction between sepsis and septic shock occurs when hypotension progresses to the point of requiring medications such as vasopressors to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg and a serum lactate level of ≥ 2 mmol/L.[9] These criteria were found to have in hospital mortality percentages in excess of 40% and were therefore considered by Sepsis-3 as a good threshold for the beginning of the "shock" state.[9] This updated definition was designed to not only reflect advances in understanding of the disease over the last 20 years but also foster unanimity as well as a common lexicon moving forward. This will enable researches and medical professionals to have a collective platform and terminology to further the efficiency and quality of sepsis treatment.[9]

Incidence:

Recognition of sepsis as a global health concern has led to many studies attempting to assess its global incidence and its widespread effect on people's health.[3] A study utilizing worldwide epidemiologic data estimated that over 31 million people are affected by sepsis each year.[12] They also found that almost 20 million of those people would qualify as having signs of septic shock characterized by organ dysfunction and more significant risk of death. With mortality rates at 17% for sepsis and 26% for severe sepsis according to their data sets this predicts that approximately one in four people who acquire sepsis are likely to die as a result.[12] This translates to upwards of 5 million deaths worldwide per year. The same study also highlights that these numbers are likely conservative as data from lower and middle income countries is often limited and difficult to collect.[12] Furthermore, these developing countries may experience a greater number of cases with higher mortality rates due to decreased access to medical care, antibiotics, and poor living conditions. All of these factors make fighting the infections that lead to and cause sepsis more difficult.

According to CDC data, sepsis did not even make an appearance on the list of leading causes of death in the US for 2016.[13] Heart disease, cancer, accidental death, chronic respiratory disease, stroke, Alzheimer's disease, diabetes, influenza/pneumonia, renal disease, and suicide rounded out the top 10.[13] Some of this can be attributed to categorization technicalities, for example influenza and pneumonia appear on the list and can often be the precursor to sepsis. In spite of its nonappearance on this list, statistics show that sepsis places a rather large burden on our healthcare system. In the face of sepsis only accounting for 3.6% of hospital stays in the US during 2013 it accounted for more than 6.2% of national healthcare expenditures with an estimated 23.663 billion dollars in aggregate healthcare costs.[14] This makes sepsis the most expensive condition noted among US hospitals.[14] The next closest condition, osteoarthritis, only accounts for 16.520 billion dollars of national healthcare costs.[14] When considering average cost per hospital stay, sepsis is almost double that of many other serious conditions and it is the number 1 cause of hospital readmissions for Medicare patients and the number 5 cause for privately insured patients in the US.[15,16]

Etiology:

As described above by the Sepsis-3 definition, sepsis occurs when there is a dysregulated response to an infection within the body. In this manner sepsis can be sourced from any type of local infection that goes untreated. The most common sources for sepsis include urinary tract infection (UTI), pneumonia, infections to abdominal organs, and infections in the pelvis.[17,18] Respiratory infections including pneumonia are the biggest contributor by far accounting for nearly half of all sepsis cases.[19] Due to this fact, sepsis is difficult to treat and can affect the body in many different ways depending on the original source and variety of infecting bacteria. When patients diagnosed with sepsis are evaluated to determine the infecting organism, blood cultures are drawn and sent to the lab for analysis. One of the most important considerations is the class of bacteria present as this guides which antibiotics will be most effective in treating it. One study found that the proportion of septic patients that were positive for gram-positive bacteria versus gram-negative bacteria was comparable. Gram-positive bacteria accounted for 47% of cases, whereas 62% were shown to have gram-negative bacteria, and another 19% were shown to be positive for fungus.[18] The fact that these percentages exceed 100% indicates that patients may test positive for two or more types of pathogen. Data from this same study also suggests that site of infection, as well as organism, can have an effect on mortality rates.[18] Other studies cite that Gram-positive infections are a more common cause of sepsis. For example a retrospective data analysis of patient records from 1979-2000 showed that approximately 52.1% of sepsis cases were caused by gram-positive bacteria, while 37.6% were caused by gram-negative bacteria and only 4.6% were fungal in nature over that time period.[20] These statistics are taken from data sets that are somewhat older. It does indicate a large amount of variation in the microorganisms that are thought to influence the disease process.

Specific antibiotic therapies are generally outside the scope of this thesis that focuses on EMS and ED integration of care. In these stages of sepsis treatment, emphasis is placed on quick identification and diagnosis as well as initial resuscitation techniques. This may include broad spectrum antibiotics which are covered later on. It is vital to begin the pathogen identification process during early initial evaluation. This includes collection of blood cultures as well as source control measures which will also be covered in other sections of this paper.

Pathophysiology:

One of the hallmarks of sepsis is a dysregulated immune response to an infection or infectious process. During normal infection, the body responds with a number of different immune based cells in order to control and eliminate the contagion. However, many of these cells become dysregulated in sepsis. The body's first response to a localized infection is to recruit local or resident macrophages. Upon arrival at the site these macrophages release inflammatory factors such as chemokine ligand eight (CXCL-8), tumor necrosis factor (TNF), and multiple interleukins.[21] These signals are designed to be received by endothelial cells located in the walls of blood vessels. The cellular response to this signal is an upregulation of adhesion molecules on their luminal surfaces. These adhesion molecules recruit even more immune cells to enter the area from the bloodstream including neutrophils whose role is to further scale up the response via the release of more Interleukin (IL)-1 beta.[21] Often in sepsis this response and the subsequent recruited cells become dysfunctional. [21] Elevated neutrophil levels are required to combat infection however they can become overactive in the case of sepsis leading them to potentially damage host cell tissues.[22] It was found that early in sepsis a large amount of IL-10 is produced by neutrophils. This is initially beneficial but overproduction of IL-10 leads to perpetuation of the dysregulated immune response.[23]

Monocytes are another important immune cell recruited to sites of infection. They are responsible for reduction of inflammation, perpetuation of healing, and clearing of pathogens via phagocytosis.[21] In sepsis, the function of these cells is also altered by multiple mechanisms and signaling cascades that are not completely understood.[24] In many models it has been shown that monocytes have a diminished ability in sepsis to release proinflammatory cytokines due to endotoxin tolerance.[25] This leads to lower levels of antigen presentation and subsequently lower levels of antigen specific lymphocyte production while simultaneously promoting inflammation therefore worsening the dysregulated immune response and infection.[25]

Further complicating sepsis is a reduction in the effectiveness of the patient's adaptive immune system which typically recognizes and coordinates defense against specific pathogens. This is due to a drop in the number of lymphocytes caused by apoptosis of both CD4 T cells and B cells. It is suspected that this is why patients experience a decrease in immune response once sepsis progresses to a certain point.[26] The next step in the sepsis pathway is related to dysregulated or dysfunctional coagulation pathways. This is primarily caused by disruption of the pathways via inflammatory cytokines that lead to an increase in tissue factor (TF) expression and down regulation of antithrombin, protein C system and fibrinolysis. Variation in the levels of these factors leads to an environment that favors coagulation.[21] When TF is upregulated it leads to upregulation of both extrinsic and intrinsic coagulation pathways. Antithrombin, which usually inhibits thrombin and clotting is also down regulated.[27] Together all of these factors come together leading to inflammation, immune system dysregulation/ suppression, and eventual systemic organ failure and hypotension. This process is outlined in Figure 2. For these reasons many of the novel therapies in development look to specifically take advantage of these pathways and correcting their dysfunction to combat the progression and mortality of sepsis.[21,25]

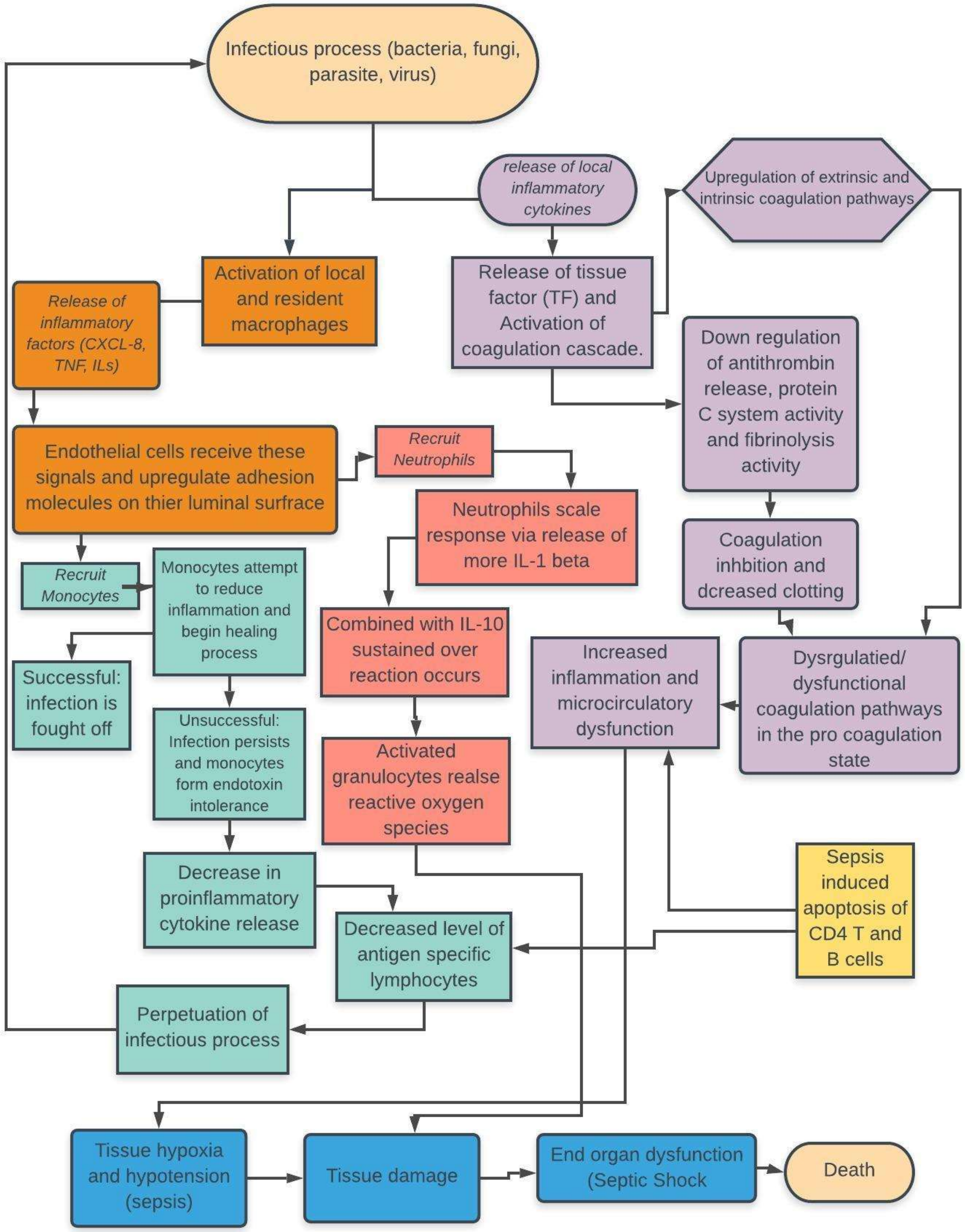

Figure 2: Flow Chart of Sepsis Pathophysiology**:** Chart outlining the general cellular processes and mechanisms that occur to create sepsis conditions in patients. Information gathered from multiple sources.[21–27]

Risk Factors:

When considering risk factors of sepsis anything that increases a patient's chances of getting an infection or diminishes a patient's ability to combat an infection may be considered. In particular, the elderly population is at an increased risk of sepsis as they have increasing immunosenescence, as well as a generally higher number of comorbidities. Additional diagnostics are hampered due to many of the signs and symptoms being attributed to these other conditions.[28] Elderly people also live in places such as nursing homes, or assisted living type facilities where it may be easier to obtain an infection.[29] Infections such as UTIs and respiratory tract infections, two of the most common infections that lead to eventual sepsis, are found in increased prevalence in the elderly population as well.[30] Those with compromised immune systems also tend to be at higher risk as their immune system cannot prevent the spread of the infection to a systemic level. This will eventually lead the patient to septic shock.

A 2004 study found that sepsis is a common complication associated with cancer and that cancer patients see an increase in sepsis incidences due to the patients' decreased immune function. It was also found by the same study that 8.4% of all cancer deaths occur as a result of sepsis complications.[31] Diabetic patients are also thought to have an increased risk of contracting sepsis as a result of the effects the condition already places on the immune and inflammatory response system. This is further complicated by decreased healing ability and the increased possibility of late identification of local infections.[32]

CLINICAL RECOGNITION/MEANS OF RECOGNITION

Sepsis is characterized primarily by an infection that progresses to the point of affecting normal organ function.[9] As this is the nature of the illness most diagnostic measures aimed at allowing early recognition are vital signs and lab tests that identify infection or organ dysfunction. As the signs of sepsis can vary depending on what organ system is affected it is challenging to derive one or two definitive measures to identify it. Originally SIRS was used as a measurement for sepsis but limitations in specificity were found.[11] SOFA and qSOFA scores are now the new standard for evaluation of sepsis patients in the hospital. These scores address the limitations of the previous SIRS criteria by considering more body systems and potential signs. (Table 1 and Table2).

Vital Signs:

***Temperature Variation**:* One important vital sign often considered as part of solving the sepsis puzzle is internal body temperature. Temperature changes are widely accepted as a sign of underlying stress to the body, thermoregulation imbalance, and possible infection.[33] A worldwide cohort study on the epidemiology and determinants of outcomes of hospital acquired blood stream infections in intensive care (EUROBACT) survey conducted of ICUs in different parts of the world found that 93% of respondents would utilize a new change in a patient's internal body temperature as a trigger to perform new blood cultures and tests, demonstrating that it can be an effective means of raising concern of a new infectious process.[34] Despite this it should not be utilized as a means of diagnosing sepsis or general infection without the supporting evidence of other factors. Some studies have found that pyrexia (elevated temperature) can manifest due to a number of conditions not all of which include infection.[35] In addition to these considerations other research by Kushimoto et al. also shows that some septic patients will present with hypothermia in contrast.[36] In these patients there is a strong indication that this particular finding signifies an even higher mortality rate than normal. Patients with an internal body temperature less than or equal to 35.5 degrees Celsius see in-hospital mortality rates rise to 52.2% according to their study.[36] It is worth noting that this study was done with patients who had already been diagnosed with both sepsis and hypothermia as they were examining hypothermia as a means of predicting in-hospital mortality, rather than sepsis incidence.

Hypotension: Hypotension is largely regarded as one of the classic, telltale signs of sepsis when coupled with other common signs and symptoms discussed in this section. Despite being such an integral part of sepsis diagnosis and supportive treatment, the causes of hypotension are not completely understood and are under active investigation. A review done in 2014 suggests that although it is likely a combination of factors, cellular dysfunction in both the immune system and in the local vasculature typically disrupts the body's normal ability to control microcirculation in the periphery.[21] This can lead to porous vessels and dilation. This dysfunction occurs specifically in lymphocytic, phagocytic, and endothelial cells and when coupled with an increase in soluble inflammatory mediators as well as coagulation cascade dysfunction the body's normal ability to prevent hypotension is inhibited.[21] A study published in 2015 by Sato and Nasu also showed that the increase in systemic endotoxins and cytokines typical of sepsis can lead to sepsis induced cardiomyopathy, which decreases ejection fraction and leads to ventricular dilation.[37] This could also contribute to hypotension in septic patients. No matter the cause, hypotension has been identified as a critical marker of sepsis and is included in the large majority of current guidelines for diagnosis both in the ED and in EMS. The new criteria place particular emphasis on maintain a MAP of 65 mmHg or greater as this represents end organ perfusion in a much more complete metric as opposed to metrics based on systolic or diastolic pressures.

Tachycardia and Tachypnea: Tachycardia and tachypnea can occur in sepsis secondary to hypotension. As perfusion pressure falls in the body peripherally, the natural response is an attempt to improve cardiac output by increasing heart rate (tachycardia). Similarly, as perfusion falls and oxygenation of tissues decreases paired with an increase in CO2 and subsequent acidic conditions in the blood, the body attempts to compensate by increasing respiratory rate resulting in tachypnea. Tachycardia and tachypnea can also be caused by a fever which commonly occurs in the presence of infections as previously discussed. These two vital signs are also associated with respiratory infections, the most common cause of sepsis.[30] One 2017 study found that persistent tachypnea and tachycardia can be associated with increased mortality in the ED. [38]

End tidal CO2 Monitoring/Capnography: End tidal CO2 (EtCO2) monitoring is one of the novel vital signs that is gaining traction as a quick non-invasive and relatively reliable marker of potential sepsis and other metabolic dysfunction in the body. EtCO2 is a measurement of the partial pressure of CO2(PCO2) in the air a person is exhaling. It is a product of cardiac output, pulmonary function, and the metabolic status of the patient.

Pulmonary function, metabolic status and therefore PCO2 can be affected two-fold in sepsis due to the existence of decreased cardiac output as well as metabolic dysfunction associated with decreased perfusion and the actual infection. [21] As sepsis worsens, blood lactate levels increase and metabolic acidosis ensues. Due to the acid base buffer system which utilizes exhaled CO2 as a way to regulate acid base balance, patients hyperventilate as a compensatory mechanism to breathe off extra CO2 and restore normal pH levels.[39] Thus EtCO2 can be measured and accurately identifies both metabolic acidosis[40] and sepsis.[41] A study done by McGillicuddy et al also found that EtCO2 monitoring shows a positive correlation between lactic acidosis and higher SOFA scores, the gold standard of diagnosing sepsis.[42] Furthermore when these readings are compared to mortality rates and lactate production they show a significant association and therefore may be usable as an early predictor of in hospital mortality for patients with sepsis.[43] In light of the close associations with other common indicators of sepsis, as well as its ability to predict hospital mortality, end tidal CO2 monitoring is becoming standard across the board when assessing patients. Normal readings of EtCO2 for a healthy patient are typically between 35-45 mmHg whereas sepsis patients are typically found to have EtCO2 readings of < 35mmHg.[41] Mortality increases as this number decreases further due to a lower value representing increased hyperventilation and compensatory effort by the patient to correct underlying metabolic acidosis.[41] It is also regarded as a non-invasive yet accurate way to assess pCO2 as it can be done with a nasal cannula.[44]

Laboratory Values:

Lactate/ Lactic Acid: The new definition and criteria for sepsis put forth by the third international consensus includes serum lactate levels of >2mmol/L as a means of diagnosing sepsis and therefore it is a focus moving forward.[9] Lactate is produced by cells when they experience conditions of hypoxia and are forced to go through anaerobic metabolism. Sepsis commonly produces hypoxic conditions either due to inflammation or hypotension.[45] When vasopressors are applied it can also increase lactate further due to vasoconstriction and subsequent hypoxia. When septic shock leads to decreased organ function in the liver and kidneys it also increases lactate levels, as this is normally where lactate is cleared.[46] Likely due to a combination of these factors, lactate has been shown to be a very reliable means of assessing sepsis patients when coupled with BP, EtCO2, heart rate, and other assessments.[47] Also advantageous is the ease at which a lactate reading can be obtained at the bedside of the patient. Handheld meters that work similarly to glucometers utilized in blood glucose measurements are becoming much more commonplace in hospitals. Theses handheld lactate meters utilize a small amount of blood obtained from a finger prick or IV start in order to analyze blood lactate levels and can produce a reading in under a minute.[48] The speed and frequency at which these readings can be obtained should help providers to afford better recognition and treatment based on real time data from the patient. The cost of these meters and point of care (POC) lactate monitoring has also been proven to be largely cost effective. A study published in 2016 found that on average normal lactate monitoring via standard laboratory methods costs approximately $33.20 per patient whereas the POC lactate monitoring cost approximately $39.53 per person.[49] This increase of $6.33 per patient produced an improvement of 1.07 additional quality adjusted years in patients proving that POC lactate is a worthwhile, meaningful, and cost effective treatment in the treatment of sepsis.[49]

Other Important Lab Values:

When a septic patient arrives at the ED, they often undergo a full panel of blood tests which includes many other individual values that can help diagnose specific organ dysfunction and other problems. A few lab values such as procalcitonin and C-reactive protein have also gained attention as potential indicators of sepsis and have seen degrees of initial testing and use in the ICU. However, they are not currently commonplace.[50] In addition, these values are not able to be used in the prehospital or urgent setting at the moment and therefore they are currently beyond the scope of this thesis.

CURRENT HOSPITAL MANAGEMENT STRATEGIES:

As established previously in this thesis, sepsis research has exploded over the past decade (Figure 1). As a result, many healthcare systems have started to adopt protocols that utilize many of the research breakthroughs to aid in the care of patients. Despite this, there is still a large amount of variation in treatment protocols, algorithms, diagnostic criteria, and standard interventions. These also vary depending on the location and healthcare organization being considered. Due to the lack of standardization many places such as New York State have started mandating that all hospitals must adopt some form of sepsis protocol as well as systems for reporting rates of sepsis diagnosis and compliance with the mandate.[51] This response is aimed at many healthcare systems which are still lagging behind in the treatment metrics of sepsis laid down by Sepsis-3. Failure to implement these new practices is leading to decreased sepsis recognition and therefore increased mortality rates despite the fact that a large consensus among care providers of the "best practices" has been reached.[52] Most healthcare agencies with newer guidelines have taken the suggestions from the Surviving Sepsis Campaign and utilized the new definitions set forth in the previously reviewed Third International Consensus.[9,52,53] Therefore the following sections exploring current hospital treatment are based primarily on these two guidelines.

Initial Resuscitation:

Initial resuscitation recommendations are typically associated with early recognition and assessment, followed by collection of blood cultures and lactate, and then finally preliminary treatments including broad spectrum antibiotics as well as fluid resuscitation. Commonly this is grouped into something referred to as a care bundle.[52] The initial fluid bolus recommendation is 30mL/kg of crystalloid fluid, such as sodium chloride solution at 0.9% concentration (normal saline), within the first 3 hours. This gives clinicians enough time to finish specific assessments and a treatment plan without delaying the initiation of treatment.[53] It is also accepted that after initiation of interventions to support blood pressure, the goal should be maintaining a MAP above 65mmHg.[54,55] Finally, is a good indicator of sepsis and is seen as a guide to assessing severity and determining treatment aimed at decreasing mortality.[56] Blood cultures are typically taken at the same time as it is necessary to obtain the results of both of these tests as soon as possible. This prevents delay of therapy and begins the analysis process so that further down the treatment algorithm more specific end goal directed therapy can take over. It is also suggested that these readings be taken prior to the initiation of treatment so that an accurate reading of initial disease severity, as well as a clear picture of the infecting organism, are obtained prior to the effects of intervention.[52] One study found that sterilization of these cultures can occur only shortly after antibiotic administration, and therefore there should be a balance of attempting to obtain these cultures before administration of interventions while at the same time not delaying this treatment. [57] Obtaining blood cultures earlier is also shown to lead to quicker phasedown of broad-spectrum antibiotics.[58–60] This is especially beneficial in decreasing overuse of antibiotics that are nonspecific or ineffective on a particular infection. As a result there is a smaller chance of developing multidrug resistant organisms, patients tend to see better outcomes with less side effects, and the overall cost and burden on the healthcare system is decreased.[59,61] The final part of the initial care bundle is the administration of broad spectrum antibiotics which also becomes a careful balance for clinicians. The Surviving Sepsis Campaign's recommendation is to consider all of the following when choosing an antibiotic treatment strategy: "the site of the initial infection and the typical pathogen profile associated with it, the presence of immune system suppression or malfunction in the specific patient, typical pathogens seen in the facility, their resistance patterns, and the other comorbidities of the patient."[52] Although many are wary of the negative effects of over-prescribing antibiotics and creating "superbugs", the SSC suggests that over inclusiveness, when it comes to prescribing broad spectrum antimicrobials in sepsis, is suggested due to the disease's severity.[52,62] The most common of these initial dosing regimens is a carbapenum based antibiotic or an extended range penicillin combined with a beta-lactamase inhibitor. These are also commonly paired up with cephalosporin specifically one that is of third generation or higher.[52] This seems to cover most infections but should be adjusted based on specific information about each case.[52] It is also worth noting that this combination therapy is recommended for initial treatment but that it is also beneficial for the patient to move to more specific therapy once the pathogen has been properly identified as prolonged antibiotic therapy can lead to death.[63] Antibiotic/antimicrobial administration is often grouped together with fluid resuscitation and other initial therapies as there is some evidence that antibiotics alone cannot combat sepsis entirely but that appropriate deployment of them with other interventions leads to lower mortality rates around 13%.[64]

Infection Source Management:

After this initial treatment bundle or strategy has been implemented, the next step is addressing the source of the infection, as well as continuation of targeted antibiotic therapy, and continual support of the patient hemodynamically. Managing the source of the infection is not always applicable but is vastly important when it comes to combating sepsis that arises from localized sources of infection such as abscesses, necrotic tissue, gastro-intestinal (GI) perforations, ischemic bowel, or kidney infections such as pyelonephritis from obstruction. These conditions cannot be treated merely by medication or supportive measures. They often persist unless physical intervention such as drainage, surgery, or debridement is done.[52] The timetable at which this takes place is very critical in patients and delays in implementation of source management can lead to increased mortality. One prospective observational cohort study in Germany found that 6 hours should be the goal for surgical source control and that anything past this significantly increases mortality in patients of approximately 10%.[65] Another study looking specifically at patients with septic shock as a result of GI perforation also found that surgery after 6 hours represents a large increase in mortality. This study actually had 100% mortality rate if source control was not done before 6 hours, and better outcomes were associated with quicker surgical intervention.[66]

Fluid Resuscitation:

As previously covered fluid resuscitation is typical among initial treatment of sepsis patients. However, there is less evidence and therefore consensus in terms of recommending fluid resuscitation after initial treatment bundles have been completed. It was found in a retrospective case study that in many cases where fluid resuscitation efforts caused positive fluid balance or volume overload patients seemed to experience higher mortality and worse outcomes therefore clinicians should be cautious to over administration of fluid post initial treatment.[67] On top of the timing for fluid administration, there is also some investigation being done into the possibilities of different types of fluid being utilized. Most studies when comparing different choices for fluid resuscitation have found that crystalloid fluids are the gold standard. Albumin has also been considered as an equivalent means of resuscitation due to a multicenter open label trial in 2014 found that there is no difference in 28 or 90-day mortality when patients are given albumin and crystalloid therapy as opposed to just crystalloid.[68] Despite this albumin has not yet made its way into many treatment protocols as studies have shown no definitive benefit to simple crystalloids. Other fluids have also been tested but are currently not recommended as they have been found to be less helpful or even harmful when compared to standard crystalloids in septic patients.[52]

Vasopressor Administration:

When initial fluid resuscitation is not enough to restore normotensive blood pressures in patients experiencing septic shock, clinicians often turn to vasoactive agents as a means to counteract the hypotension. This is not required in all cases but is commonplace to avoid requiring administration of excessive amounts of fluid that could potentially cause complications as noted in the previous paragraph. In this class of drugs there are multiple options including but not limited to epinephrine, dopamine, norepinephrine, dobutamine, vasopressin, and levosimendan.[69] The two most widely used and studied, by far, are norepinephrine and dopamine with each offering slightly different effects.[70] Norepinephrine has been found to be beneficial in the majority of patients due to its higher specificity in increasing vasoconstriction and increasing systemic vascular resistance with little effect on heart rate and stroke volume, compared to dopamine. A separate meta-analysis was able to show that norepinephrine has a significantly lower risk profile of around 11% in sepsis treatment. The study stated that, "when compared to dopamine, norepinephrine produces a greater reduction in mortality, cardiac events, and heart rate while being more effective in raising systemic vascular resistance", showing that it is all around a better medication for sepsis in most situations.[71–73] In a review of multiple trials epinephrine, vasopressin, phenylephrine, and terlipressin were all compared to norepinephrine and dopamine in terms of effectiveness in reducing mortality in septic shock. These trials found that there is no significant change in mortality in any of these medications when compared to the two typical first line drugs of norepinephrine and dopamine.[73] As a result of this norepinephrine and dopamine are still recommended as they are the most focused of all of these medications. The same study also showed that norepinephrine should be utilized over dopamine when they are directly compared to one another due to less side effects associated with a more focused mode of action hemodynamically. Norepinephrine was shown to have approximately half the risk of causing other complications such as cardiac arrhythmias among other effects and is therefore still the recommendation for a first line vasopressor in sepsis.[73] Other vasopressors are viable options in cases when norepinephrine is unavailable or contraindicated however they are generally regarded as less favorable. There are certain cases where other vasoactive agents such as dopamine, dobutamine, and levosimendan are theorized to be more favorable to treat some sepsis cases however these incidences are generally recorded in a low number of patients and the data available to support their alternate use comes from only a few small trials. Due to its complexity, this usually is up to the individual discretion of the treating physician and not outlined in hospital protocols.[52]

Blood Pressure Monitoring:

Once the initial resuscitation of a septic patient has begun and the patient has been admitted to the ICU for continued treatment and recovery it is also recommended by the SSC that a central arterial catheter be placed so that blood pressure may be monitored by IBP (Invasive Arterial Blood Pressure) vs NIBP (Non-Invasive Blood Pressure). IBP is generally regarded as a more accurate method of measuring blood pressure in real time and possesses less possibility for inaccuracy. A 2013 study of ICU patients found that there is a significant discrepancy in pressures when comparing IBP and NIBP in terms of systolic and diastolic measurements. They found typically that NIBP reading read lower than true IBP in situations of hypertension whilst reading higher than IBP in situations of hypotension. The study also revealed that despite this discrepancy there were not significant differences in MAP between the two methods and suggested this as an improved marker of patient condition as opposed to systolic and diastolic readings especially when utilizing NiBP.[74] As covered previously in the initial resuscitation section the SSC has already recommended that MAP be the standard vital sign in sepsis target blood pressures as opposed to systolic and diastolic readings. This is especially important to consider in areas where IBP may not be available or feasible such as prehospital EMS. IBP may also be beneficial as it provides a continuous real time reading of the patient's blood pressure as opposed to a NIBP reading which takes time to be acquired. Real time IBP scores may better be able to show the results of interventions quickly and may help to lead to quicker adjustments in medication and management. In terms of EMS management some states allow advanced life support (ALS) ambulances to monitor IBP however it is not a standardized protocol in most areas.

Mechanical Ventilation/Respiratory Support:

The SSC also makes several recommendations when it comes to mechanical ventilation and sedation of patients with suspected acute respiratory distress syndrome (ARDS) and sepsis. These specific considerations are outside the scope of this paper as these decisions typically only come into practice further down the sepsis care algorithm after the patient has left EMS and ED care. Generally care in early treatment revolves around supporting the patient's ventilation and oxygenation via supplemental oxygen administration and supportive ventilation via simple BVM or CPAP and does not extend to mechanical ventilation or sedation.[52]

Other Considerations:

The SSC also identified many potential management techniques and interventions that it did not recommend, as of yet, due to lack of, or conflicting evidence. These include administration of corticosteroids, blood products, immunoglobulins, anticoagulants, and bicarbonate.[52]

HOSPITAL IMPLEMENTATION AND IMPROVEMENT MEASURES:

As hospitals evolve in their treatment of sepsis the newly set forth SSC guidelines and the newly established Sepsis-3 definitions are the primary guiding factors when it comes to setting up new protocols in individual healthcare systems. Although the SSC is very through in its considerations and suggestions it is ultimately up to hospitals to implement their own protocols. The most effective means of combating high mortality rates is improving recognition and time to initiation of end goal directed therapy (EGDT). This has been the primary focus of new sepsis treatment systems. Naturally this has led to many new protocols and efforts to change the way medical professionals approach sepsis upon first diagnosis and treatment. Due to its unique role in the hospital as the point of entry for most patients, the ED is often targeted as the area where many of these many of these new strategies can potentially be most effective. Studies have found that on average one in every three sepsis patients initially presents through the emergency department.[75] Another study in Utah found that nearly 2% of all patients that present to the ED have sepsis.[76] So far measures to increase recognition and initial diagnosis have proven to be effective in the ED. One study at a tertiary care ED found that simple implementation of a standard sepsis treatment algorithm based on SSC suggestions, paired with improved nurse education, led to a nearly a 28% reduction in mortality.[5] This treatment algorithm involved rapid diagnosis, lactate, blood cultures, labs, broad spectrum antibiotics, and a multidisciplinary team approach. The results showed that mortality rate decreased from 18.4% to 13.2% as a result of the education and algorithm. Additionally, both compliance with SSC 3-hour bundle recommendations as well as the number of patients recognized to have sepsis increased significantly.[5] A similarly designed study done in the Netherlands which also looked at nurse education, implementation of SSC care bundles, and a sepsis protocol found similar results with care bundle compliance increasing from 3.5% to 12.4%. Some individual measurements such as serum lactate saw even larger increases in compliance from 17% to 78%.[77] A third retrospective chart review also found that implementation of similar protocol measures and nurse initiated protocols led to higher compliance with SSC bundles. They also were able to find that bundle compliance with measurements such as serum lactate and blood cultures approached much higher compliance than interventions requiring coordination between multiple health care professionals. The researchers suggested further integration of interdisciplinary teams in order to further increase bundle compliance which can be implemented between nurses and physicians but also between the hospital and EMS. This study found no difference in mortality which may be a result of intervention compliance not increasing as drastically as diagnostic compliance.[78]

Before the recommendation by the SSC and Sepsis-3 EtCO2 and lactate monitoring had not been considered as widely in sepsis management. As an example of newer hospital sepsis procedures, the policies put forth at Baylor University Medical Center that revolve around two distinct care bundles. First, within the initial 3 hours and the second within the first 6 hours of care post suspicion and activation of sepsis protocol. The first 3-hour bundle includes the diagnostic tools of serum lactate as well as blood cultures, the initial treatment of a crystalloid fluid bolus, and broad-spectrum antibiotics. If patients do not improve the 6-hour bundle is implemented which is similar to the 3-hour bundle in terms of diagnostic tools but represents a more targeted and aggressive strategy when it comes to intervention. Accompanied with the recommendation of these bundles is a large amount of staff education and supplemental protocol flow charts with suggestions of next steps and interventions.[79] Other institutions such as Massachusetts General Hospital have attempted to implement computer algorithm based sepsis alert systems that trigger warnings to nurses and physicians when the lab results and vital signs of a patient meet patterns associated with typical sepsis presentations.[80]

CURRENT EMS TREATMENT STRATEGIES:

Many of the previously outlined studies highlight that increased education, focused on identifying sepsis quickly and accurately is one of the best means of combating it. As covered, this places a lot of emphasis on initial care in the emergency department which has shown improvement based on many of the methods covered in the previous section. When considering further actions that can be taken, Emergency Medical Services (EMS) has been considered one of the areas of potential further improvement. A 2010 study analyzing Medicare data estimated that approximately 36.7% of all patients who present to the ED arrive via EMS, representing a sizable portion of ED admissions.[81] When considering other time sensitive conditions, such as myocardial infarction and acute cerebrovascular accident (CVA)/stroke, implementation of increased education and specific protocols in EMS have shown benefit. These measures are focused primarily on identification and initiation of early treatment along with early hospital alert procedures and have led to improved outcomes and lower levels of mortality or serious impairment.[7,82] Another prospective study, also published in 2010 established that patients with serious infections such as sepsis or septic shock arrived at the hospital via EMS 34.2% of the time. This percentage is in line with the amount transported in general.[83] The same study also found that patients who met criteria for sepsis protocols within the ED were more than likely those who arrived via EMS with 61.1% of these patients having had initial EMS care.[83] This suggests that higher acuity Septic patients are more than likely those who utilize EMS.[83] EMS crews spend large amounts of time with these patients (i.e. upwards of an hour).[84] Despite this large percentage, current recognition of sepsis via EMS is poor. One pilot study utilizing lactate meters and other criteria only showed an accurate severe sepsis recognition rate of 47.8%.[85]

Levels of EMS care:

Similar to sepsis the nationwide EMS system has seen a large evolution over the last two decades. Historically, EMS agencies have been managed independently at the regional and state level with these smaller governing bodies handling everything in house. This includes all licensing, training, establishment protocols and standards of care, regulation, and logistical concerns of a particular geographical area. This meant that in many cases the established standard of care in terms of any particular disease including sepsis, varied largely in different parts of the country or even in different parts of the same state. Again, similar to that of sepsis treatment, there has been considerable effort to standardize and improve EMS care across the country through best practices. The National Registry of Emergency Medical Technicians (NREMT) which was established in the 1970s, has slowly started to integrate itself into all states across the country and has nationalized many aspects of the field.[86] Currently all initial training, licensing examinations, recertification and levels of EMTs are defined by the NREMT. They also suggest certain protocols and best practices, but still leave individual protocol decisions and the exact implementation of care to regional and state agencies. Despite this, most states have come to accept the four standardized levels of care that exist within EMS put forward by the NREMT. These include Emergency Medical Responder (EMR), Emergency Medical Technician- Basic (EMT-B), Advanced Emergency Medical Technician (AEMT), and Emergency Medical Technician- Paramedic (EMT-P) with each representing a different level of education as well as capability. EMR level EMS personnel are trained in very basic lifesaving first aid as well as CPR. Those registered as EMRs are not usually individuals staffing ambulances but other first responders such as firefighters or police officers. Ambulances are also broken into two separate classes Basic Life Support (BLS) and Advanced Life Support (ALS). BLS ambulances are typically staffed by EMT-B personnel who represent the entry level EMT. These individuals are trained in CPR as well as numerous life saving techniques and are equipped to do basic lifesaving maneuvers and administer select lifesaving medications such as epinephrine auto-injectors and nasal narcan. EMT-B represent the bulk of EMTs nationwide with 283,143 individuals occupying this rank with the total certified in all ranks of 416,174.[86] ALS ambulances, typically staffed by EMT-Ps and occasionally 1 AEMT are equipped to handle more complex medical emergencies and are capable of placing IVs, advanced cardiac monitoring and intervention, intubation, and more. For a more through overview of the varying abilities see **Table 3** which is based on the Massachusetts Specific Protocols.[87] As previously stated protocols are state dependent but generally follow closely to this format as it mirrors the NREMT guidelines.

Table 3: EMS Provider Scopes of Practice

Procedures and Interventions	***Level of Care***			
Access and medication administration	**EMR**	**EMT-Basic**	**AEMT**	**EMT-Paramedic**
IM Auto-Injector medication administration	Yes	Yes	Yes	Yes
Blood Products	No	No	No	Yes (IFT)
Inhalation	No	Yes (via MDI)	Yes	Yes

Intramuscular access (IM)	No	Yes (via extra training and medical director approval)	Yes	Yes
Intraosseous access (IO)	No	No	Yes	Yes
Intravenous access (IV)	No	No	Yes	Yes
IV Medication Pump	No	No	No	Yes
Oral medication administration	No	Yes	Yes	Yes
Intranasal medication administration (IN)	Yes	Yes	Yes	Yes
Rectal Medication administration	No	No	Yes (with EMT-P assistance)	Yes
Subcutaneous (SC) Medication Administration	No	No	Yes	Yes
Sublingual Medication Administration (SL)	No	Yes (May assist patient in Self administration)	Yes	Yes
Central Line Maintenance	No	No	No	Yes (IFT)
Peripheral Venous Access	No	No	Yes	Yes
Airway/Respiratory Procedures				
Bag Valve Mask (BVM)	Yes	Yes	Yes	Yes
End Tidal Capnography	No	No	Yes	Yes
Chest Tube Maintenance	No	No	No	Yes (IFT)
Abdominal Thrusts /Heimlich (Airway Clearing)	Yes	Yes	Yes	Yes

Continuous Positive Airway Pressure (CPAP)	No	Yes (with EMT=P assistance)	Yes (with EMT=P assistance)	Yes
Endotracheal Intubation	No	No	No	Yes
Endotracheal Suctioning	No	No	Yes	Yes
Supraglottic Airways	No	No	Yes	Yes
Nasogastric/Orogastric Tube	No	No	No	Yes
Nasopharyngeal Airways (NPA)	No	Yes	Yes	Yes
Nebulizer Treatments	No	Yes (via extra training and medical director approval)	Yes	Yes
Needle Decompression	No	No	No	Yes
Oral Suctioning	No	Yes	Yes	Yes
Oropharyngeal Airway (OPA)	Yes	Yes	Yes	Yes
Oxygen Administration	No	Yes	Yes	Yes
Pulse Oximetry	No	Yes	Yes	Yes
Tracheostomy Maintenance	No	Yes	Yes	Yes
Mechanical Ventilator Operation	No	No	No	Yes (IFT)
Cardiac Interventions and Management				
12-Lead EKG placement	No	Yes (with additional training while assisting EMTP)	Yes (with additional training while assisting EMTP)	Yes
4 Lead EKG placement	No	Yes (with additional training while	Yes (with additional training while	Yes

		assisting EMTP)	assisting EMTP)	
Cardiopulmonary Resuscitation (CPR)	Yes	Yes	Yes	Yes
AED Defibrillation	Yes	Yes	Yes	Yes
Manual Defibrillation	No	No	No	Yes
Interpretation of 12-Lead EKG	No	No	No	Yes
Interpretation of 4 Lead EKG	No	No	No	Yes
Synchronized Cardioversion	No	No	No	Yes
Transcutaneous Pacing	No	No	No	Yes
Targeted Temperature Management	No	Yes (via extra training and medical director approval)	Yes (via extra training and medical director approval)	Yes
Trauma and wound care and diagnostics				
Blood draw	No	No	Yes	Yes
Blood Glucose Analysis (BGL)	No	Yes (via extra training and medical director approval)	Yes	Yes
Blood Lactate Analysis	No	No	No	Yes
Burn Care	No	Yes	Yes	Yes
Cervical Spine Immobilization	Yes	Yes	Yes	Yes
Childbirth	No	Yes	Yes	Yes
Cold Pack	Yes	Yes	Yes	Yes

Extrication	No	Yes	Yes	Yes
Eye Irrigation (Morgan Lens)	No	Yes	Yes	Yes
Hot Pack	No	Yes	Yes	Yes
Pharmacological Restraints	No	No	No	Yes
Physical Restraints	No	Yes	Yes	Yes
Selective Spinal Assessment	No	Yes (via extra training and medical director approval)	Yes (via extra training and medical director approval)	Yes (via extra training and medical director approval)
Spinal Immobilization	Yes	Yes	Yes	Yes
Splinting	No	Yes	Yes	Yes
Would Care- Occlusive Dressings	No	Yes	Yes	Yes
Pressure bandages/ Tourniquet	Yes	Yes	Yes	Yes
Wound Packing	No	Yes	Yes	Yes

EMS Provider Scopes of Practice- represents the 4 different classes of EMS professionals as well as their ability to perform specific interventions. *IFT:* Interfacility Transfers

Information gathered from Massachusetts EMS protocols [88]

As can be seen in **Table 3**, many of the interventions specifically related to the recognition and treatment of sepsis in the hospital are related primarily to ALS level ambulance service provided by AEMTs and paramedics. This can also be seen in other conditions and one study found that differing levels of EMS care are appropriate for different injuries and conditions.[89] Specifically in sepsis this includes advanced hemodynamic monitoring, capnography, lactate measurement, and IV fluid and medication administration. For this reason, many of the proposed improvements in sepsis are addressed to this level of care.

Current EMS Sepsis Protocols:

Due to the regional approach taken to EMS protocols there exists less uniformity than hospital-based care in most areas. Some agencies have adopted newer models of EMS sepsis care while others have not. Iowa, for example, which has uniform EMS policies for the entire state, last updated in March of 2018, does not mention the term "sepsis," and simply has a section that addresses distributive shock.[90] Other states such as New Hampshire have entire sections dedicated to the diagnosis and treatment of both pediatric and adult sepsis.[91] Table 4 represents many of the varying EMS protocols in use currently across the country and highlights the differences of current policies in 6 different state

Table 4: Analysis of Sepsis protocols in 6 different States

Elements of Protocol	State					
	New Hampshire: Statewide	***Massachusetts: Statewide***	***California: San Francisco County***	***Texas: Fort Worth***	***Washington: Northwest Regional***	***Iowa: Statewide***
Sepsis ID Criteria	-Suspected Infection-Yes - Evidence of Sepsis criteria 2 or more: Temperature <96.8 degrees Fahrenheit or > 101 degrees Fahrenheit, Heart Rate > 90 bpm, Respiratory Rate >20 bpm, Systolic BP <90 mmHG or MAP < 65 mmHg, New onset Altered Mental Status or increasing mental status change, Serum Lactate level > 2 mmol/L, ETCO2 <25mmHg	-Suspected Infection-Yes - Evidence of Sepsis criteria 2 or more: Temperature <96.8 degrees Fahrenheit or > 100.4 degrees Fahrenheit, Heart Rate > 90 bpm, Respiratory Rate >22 bpm, Systolic BP <90 mmHG or MAP < 65 mmHg, New onset Altered Mental Status or increasing mental status change, Serum Lactate level > 4 mmol/L, ETCO2 <25mmHg	- Do sepsis screen if patient has abnormal vital signs - Does patient have a suspected or documented infection? - Evidence of Sepsis Criteria 2 or more: - Temperature> 38 degrees Celsius or < 36 degrees Celsius - Heart Rate > 90 bpm - Respiratory rate> 20 bpm	-No Specific Sepsis protocol, listed under “shock/hypotension” page If Systolic Blood Pressure is < or equal to 90 mmHg and/or suspected high risk for infection with 2 or more of the following: RR > 20 bpm, HR >90, temperature >100.4 degrees Fahrenheit	-No Specific Sepsis protocol listed under “Non=traumatic Shock” - Hypotension, Rales and Pulmonary Edema, Altered Mental Status, weakness/dizziness, weak or rapid pulse, pale, cool or clammy skin.	- No specific Sepsis diagnostic criteria or protocol
EMT- Basic Protocol	-Routine Patient care - Oxygen administration for goal SpO2 of 94-99% - No transport delay - If positive screen notify receiving facility via “Sepsis Alert”	-Routine Patient care -Oxygen administration for goal SpO2 of 94% -If positive screen notify receiving facility via “Sepsis Alert	- Position of comfort - NPO - Oxygen as indicated	- Position patient in supine position with legs elevated as appropriate and tolerated (No Trendelenburg)	- No specific Protocols	- Maintain SpO2 of 94-99% - Place patient in Supine Position - If Temperature is > 102 degrees Fahrenheit cool patient

AEMT Protocol	- Rapidly administer 0.9% NaCl to maintain systolic BP >90mmHg or MAP of > 65mmHg in 500mL boluses. Total Volume should not exceed 4 Liters. Patients should be reassessed frequently with special attention given to lung sounds to avoid volume overload	-Full ALS assessment and treatment - Large bore IV access - IV 0.9% NaCl enroute: administer 500mL boluses up to 30mL/kg while assessing frequent lung sounds to ensure volume overload dose not occur	No specific AEMT protocol	-Normal Saline 20 mL/kg IV bolus -Titrate to improved vital signs and SBP, max of 2 Liters. Contact medical Control if not successful	- Obtain IV/IO access - Fluid Bolus of Normal Saline or Lactated Ringers 250mL-1000mL, may repeat once if no signs of Pulmonary Edema for a goal SBP of > 100mmHg	-Same as EMT-Paramedic
EMT-Paramedic Protocol	-Obtain serum Lactate level if available -If there is no adequate hemodynamic response after 2,000mL IV fluid infused consider: Norepinephrine or Epinephrine infusion	-May administer additional fluid boluses and vasopressor medications Norepinephrine, Dopamine, or Epinephrine after medical control is contacted if needed	-Establish IV/IO with Normal Saline TKO. Recommend 2 IV Lines - If Blood Glucose is <60mg/dl, unmeasurable or patient is known diabetic administer: Dextrose - For HR > 100 bpm or BP < 90 administer Normal Saline fluid bolus.	- If suspected Sepsis criteria and ETCO2 of <25 mmHg then contact receiving facility with “Sepsis alert”	- Obtain EKG and 12-Lead EKG - Consider Norepinephrine, Dopamine, or Epinephrine infusion for SBP of > 100 mmHg	- Administer 20 mL/kg up to 500mL of Normal Saline or Lactated ringers, Repeat for goal BP of 90mmHg - Consider administering Dopamine infusion - Consider administered diphenhydramine bolus.
Presence of Pediatric Protocol	Full protocol present with additional diagnostic criteria and interventions	None present	None Present	None Present	None Present	None Present

Analysis of Sepsis protocols in 6 different States Note that protocols for higher levels of care would include doing all things in lower level of care protocols. Example: EMT-P would be responsible for their specific protocol in addition to AEMT and EMT-B protocols. All information in chart was obtained through individual state EMS protocols.[88,90–94]

As can be seen in the six states in Table 4, protocols vary widely across the country. Out of the states shown, Massachusetts and New Hampshire have very developed sepsis protocols compared to those of Washington, or Iowa. However, all six states show differences in diagnostic criteria even when addressing the same vital sign or intervention. Even more concerning is the lack of standard terminology and absence of specific, diagnostic criteria in states such as Washington and Iowa. Many states do not even have specific areas of their protocol devoted to sepsis rather, they term it "non-traumatic shock" and "distributive shock" respectively. These inconsistencies make standard communication and education techniques difficult for the NREMT to coordinate between states. Providers who are certified at the same level may approach treatment, identification, and nomenclature of the disease completely differently within different regions. Sepsis-3 attempted to address this in the hospital setting as previously covered. The findings of that study have only trickled down into some of the states.

EMS IMPLEMENTATION AND IMPROVEMENT MEASURES:

Standardization/Integration of EMS and Hospital Care:

Hospital based programs that focused on standardizing and streamlining sepsis diagnosis and treatment criteria through increased education of ER nurses and implementation of specific protocols is one of the most effective means of decreasing mortality.[53] With estimates of between approximately 1/3 and 1/2 of all sepsis patients presenting to the hospital through EMS, similar efforts in the EMS space could lead to a further improvement on recognition and treatment times.[81,84] A prospective observational study in Canada found that with education and protocol implementation paramedic recognition of sepsis in the prehospital settings rose to around 27% with 78.2% accuracy. This is significant considering the control group was emergency physicians that were given no protocol and only identified 11.3% of patients with sepsis.[95] This shows that EMS providers are capable of improved identification if provided with proper tools and training.

Diagnostic Tools:

Lactate:

Serum lactate and lactic acid readings have become commonplace in hospital settings when doing a standard sepsis workup. This is for good reason as lactate has been identified as one of the most important indicators of mortality in the hospital in cases of severe sepsis.[56] Lactate has also been officially recognized in most updated sepsis protocols including the Sepsis-3 review as a very valuable sign when compared to others for consideration when diagnosing and guiding treatment.[9,47] As described in the section about hospital lactate readings, bedside POC lactate monitoring has become fairly commonplace and could be moved to EMS providers with a small investment of education and cost. Some states have already begun to implement the practice in the field and lactate readings are listed in multiple state protocols for identifying sepsis (see Table 4). Despite this lactate monitors are not mandated pieces of equipment on ambulances even in places with lactate readings in protocols like Massachusetts.[87] Initial studies in the utilization of these meters has found data that suggests elevated lactate in prehospital readings appears to correlate to higher ICU admission and sepsis diagnosis. However, no statistically significant data has been found yet and more study is needed.[85,96] Both studies cited here are small in sample size utilizing only 112 patients each. Despite this, both studies recognize that lactate monitoring, when coupled with increased education can help EMS providers identify sepsis early and more often in acute patients. [85,96]

End Tidal CO2:

Another vital sign outside of current ALS ambulance monitoring in sepsis is EtCO2. As described above, numerous studies have shown that decreased levels of EtCO2 are significantly associated with morbidity and mortality in sepsis patients and is therefore a good indicator of severity.[43] Another study found that it is feasible to take readings easily in the ED and that it is statistically associated with both SOFA scores as well as lactate levels.[42] Similar to lactate readings EtCO2 is a promising tool that can be extended into EMS because it is already a vital sign that most ALS ambulances are capable of acquiring with current equipment. EtCO2 readings are obtained via a nasal cannula, or inline meter unit (for intubated, BIPAP, or CPAP patients) that attaches to a standard cardiac monitor carried on ALS ambulances. This is typically utilized in patients experiencing respiratory distress, intubated patients, or in resuscitation situations but is not currently utilized in all patients.[97,98] The fact that this reading can be taken in a non-invasive manner makes it easy for providers to utilize in the majority of patients. A retrospective cohort study done in Florida also found that EMS is capable of taking accurate readings with the current equipment available on ALS ambulances and that independent of sepsis EtCO2 is a very consistent predictor of morbidity and mortality. For this reason, the study suggests regular use of it as a vital sign to drive assessment and care.[99] A separate prospective cohort study then looked at utilization of EtCO2 readings specifically for the diagnosing of sepsis in the prehospital setting and was able to show that a protocol incorporating both ETCO2 and other SIRS criteria was more accurate in predicting sepsis and was therefore suggested as a way to decrease time to interventions.[100] Of the current EMS protocols reviewed in this paper 2 out of the 6 have ETCO2 listed in potential diagnostic criteria for sepsis which shows some potential room for improvement. (Table 4)

ALS Monitoring:

In addition to EtCO2 and lactate monitoring, EMS personnel can obtain a large number of vital signs and diagnostic information through their normal assessment strategies. These items include heart rate, blood pressure (including MAP), pulse oximetry, blood glucose, cardiac rhythm, 12-Lead EKG, temperature, and respiratory rate. Many of these vitals as shown in the Table 4 criteria and have found their way into the protocol for sepsis diagnostic criteria. These core vital signs should be obtained by all ALS ambulance crews on any patient with significant signs of injury or illness. It has also been hypothesized that arming EMS providers with education on SOFA or qSOFA scores would be beneficial in identifying patients who may be septic. These scores were specifically developed to be a simplified and quick way of assessing patients and most vital sign criteria required can be readily obtained via normal EMS monitoring techniques. However, they have not yet been tested in this setting and therefore the effectiveness is not yet known.[101]

"Sepsis Alerts":

Many potential interventions have been suggested in efforts to improve EMS's involvement in the sepsis care pathway. However, there is currently not a large amount of supporting data to show that any of these suggestions are truly effective. A systematic review of studies done in the field was completed in 2016 and showed that most improvements in outcome that result from EMS do so by improving the process of the patient being admitted to the hospital. This accelerated the patient's recognition and treatment on arrival.[102] A retrospective cohort study from Australia in 2013 showed that EMS often transports the most critically ill sepsis patients. Therefore this continuity of care is especially important for these patients.[103] Another prospective data analysis of approximately 1000 severely septic patients in Philadelphia showed that, on average, arriving via EMS improved the time interval between hospital arrival and initiation of antibiotic and IVF treatments. EMS patients received antibiotics at 116 minutes vs 152 minutes for non-EMS arrivals.[104] This study also attempted to compare mortality which showed no statistically significant difference between EMS and non-EMS arrivals however the results were not adjusted to account for the fact that the EMS population often is sicker than those who self-admit to the ER.[103] This acceleration of the sepsis care is important as definitive end goal directed therapies and early initiation is a key factor in long term outcomes. Many states with further developed prehospital sepsis protocols, represented by Massachusetts and New Hampshire in Table 4, have instituted "Sepsis Alerts" which refers to an alert given by radio or phone to the receiving hospital by the EMS crew prior to arrival. The concept is that if a patient meets all sepsis criteria in the field and is suspected to have sepsis this method can let the hospital know ahead of time to have a team ready to perform a quick analysis of the patient upon arrival and subsequently initiate therapy. This protocol can drastically decrease the time required for the patient to be triaged and fully assessed by hospital staff. Similar methods have been utilized effectively in integration of EMS and hospital care with other time sensitive conditions such as CVA, or myocardial infarction.[7,8] No studies have evaluated the effectiveness of these alert protocols specifically in sepsis as of yet. None the less, sepsis protocols are beginning to become more common in more progressive EMS systems.

EMS Treatment Options:

Intravenous Fluid Administration:

It has been previously established that rapid initiation of end goal directed therapy in patients with sepsis is the most effective way to combat the disease, however in the prehospital setting there is very little evidence of the effectiveness of interventions outside of rapid assessment, care, and transport to the hospital thusfar.[102] Despite this many EMS protocols involve some sort of intervention or supportive measures at the very least when a patient appears to meet sepsis criteria. (Table 4) One of the staples of sepsis management is the administration of IV fluids as previously covered.[53] This is often done to combat hypotension seen in most septic patients and has been shown to be effective in decreasing mortality when done in the pre-hospital setting. A 2014 prospective data analysis of sepsis patients transported via EMS in King County, WA showed that patients who either just had an IV placed or had an IV placed and received IVF via EMS were associated with a reduction in the chance of organ failure once hospitalized.[105] This study along with a secondary data analysis of a retrospective cohort study done by the same research team on patients in a Pennsylvania tertiary care facility showed low levels of both IV access as well as IVF fluid administration in septic patients.[105,106] The Pennsylvania study showed IVF therapy was initiated via EMS in only 48% of patients who presented with sepsis. When considering those who were also hypotensive upon arrival at the ED still only 64% of them received IVF.[106] The other study, done 4 years later, showed somewhat lower percentages in terms of IVF administration and IV placement. It is worth noting that a different study design and different EMS system was utilized here. The results showed that 70% of patients with Sepsis did not receive IVF or IV placement via EMS and that in the 30% that did have an IV placed only 23% received IVF.[105] These numbers show that there is significant room for improvement when it comes to this particular intervention. All the equipment and skills necessary to complete IVF crystalloid fluid administration that is recommended in the Sepsis-3 and SSC guidelines is already available in ALS ambulances nationwide and is a standard of care in cases of hypotension and shock.[9,52] Increasing education and awareness for its specific use in sepsis along with earlier initiation is key in improving these metrics.

Antibiotic Administration:

Similar to IVF administration, antibiotics as previously discussed are one of the essential aspects of EGDT in the treatment of sepsis. As recommended in the SSC sepsis is combated by first administering broad spectrum antibiotics and then tapering these down to a more focused approach once the infection causing organism is discovered.[52] This helps to directly attack and eliminate the infection and decreases the odds of adverse effects while also decreasing the chance of developing antibiotic resistant microorganisms. Literature regarding the importance of antibiotic timing is mixed. A prospective clinical trial done in 2009 in Australia for example showed that treatment of patients with antibiotics in EMS according to a guided protocol led to a reduction in the delay of antimicrobials once in the hospital and also reduced 28-day mortality.[107] On the other hand, one large prospective study of ED patients at three different tertiary care centers in different states showed no "increase in mortality with each hour delay to administration of antibiotics after triage".[108] This conflicting evidence reveals the need for more research and study in this area. There also has not yet been any studies done to assess the validity of doing such treatment in the United States via EMS. For the time being quick administration of broad-spectrum antibiotics will continue to be utilized in the hospital setting under the Sepsis-3 and SSC guidelines. If more trials of antibiotics in EMS are successful elsewhere in combating sepsis policy makers may revisit it as a topic. Until then, it is unlikely that it will be seen in United States EMS.

Vasopressor Administration:

The final piece of EMS sepsis treatment algorithms currently utilized in each state is the use of vasopressor medications in situations where IVF administration is either non-effective in combating hypotension or it is contraindicated due to issues such as pulmonary edema. Most EMS protocols (Table 4) advise administration of substantial IVF first before vasopressors are considered. Some states such as Massachusetts, require consultation with a medical control physician before proceeding with vasopressor therapy as it can produce negative side effects in many patients. Multiple studies have shown that in most sepsis cases, the preferred vasopressors are norepinephrine first and dopamine second.[109] In most states ALS EMS crews are already equipped with both of these medications and are already trained in their administration. This is a good option to have available in case of need for immediate resuscitation of a patient in critical septic shock for hemodynamic support. However, there is little to no data on the effect of EMS vasopressor therapy on mortality or survivorship of sepsis.

Other considerations:

BLS ambulance care:

As sepsis is a serious illness that can lead to death, the majority of the diagnostic criteria, considerations and potential interventions for pre-hospital sepsis management have been focused on ALS ambulance service provided by EMT-Paramedics and AEMTs (Table 3). It has been established that septic patients would qualify as appropriate for ALS level of care as more serious conditions such as this require a higher level of monitoring and intervention.[89] Despite this, only about half of sepsis patients transported by EMS do so via paramedics with the other half transported via BLS.[84] Thus, it could be beneficial for EMS systems to implement protocols that address BLS care as well. Numerous protocols (Table 4) allow BLS to use the same diagnostic criteria and do supportive therapies as they are capable such as oxygen administration. However, much of the EMS related sepsis education is aimed only at ALS providers. Improved BLS education could at least provide these individuals with the ability to recognize potential signs of sepsis and then get the patient to the appropriate level of care more quickly.

Community Paramedicine:

Another exciting innovation in the potential future of EMS sepsis prevention, treatment, and integration with the hospital is the novel idea of community paramedicine. Community paramedicine programs look to train EMT-paramedics and EMT-basics with additional skills that allow them to provide many of the services patients normally have to travel to the hospital or primary care physician to receive. This can include screenings and tests, including those for the early signs of sepsis or other infection, follow up care after hospital discharge to prevent readmission, or even drawing blood for lab work, all in the patient's own home.[110,111] Healthcare systems are experimenting with these services as they have the ability to decrease hospital admissions and readmissions and cut costs on top of improving patient outcomes. These interventions can address patient needs before they progress to the point of requiring hospitalization. With many programs still in their pilot phases, there is little data available thus far on the effectiveness of these programs.

CONCLUSION:

This thesis has described many of the changes in the ever-evolving field of sepsis care and research. The medical community has progressed immensely in the treatment and understanding of this serious disease due to increased interest, innovation, and forward thinking on the part of scientists and medical professionals alike. When it comes to consolidating all of the new information into care suggestions designed for improvement of both care and mortality rates the healthcare community has done a fairly thorough job in updating definitions and protocols as represented in the Sepsis-3 consensus and Surviving Sepsis Campaign respectively. These campaigns have come to recognize that the key to effective treatment is prompt recognition and initial treatment followed by end goal directed therapy. As this is the gold standard, many developments have focused on means to improving these metrics. Many healthcare systems have done a great job of implementing these types of developments. This includes the use of novel vital signs and tests, such as POC lactate monitoring and ETCO2, to increased education and awareness, as well as protocol-based treatments for improved efficiency. More standardization could still be accomplished in these hospital programs, but substantial progress is being made. Despite this, there is still a large opportunity for improvement available in terms of interface and integration of care between the hospital and the EMS community in sepsis treatment. Many of the changes that have shown positive results in the hospital could be explored or utilized in an ambulance. This thesis has covered how many of these changes could be implemented. It suggests that moving forward pre-hospital providers look to standardize protocols under the NREMT to bring more thorough sepsis protocols to states currently lacking them. In addition, they should adjust existing criteria to reflect those generally utilized in hospital systems. These protocols should offer explicit diagnostic criteria and clear protocols that focus on fast assessment and transport to medical care capable of EGDT with measures to expedite the care in the hospital such as “sepsis alerts”. Increased education and awareness programs are also required to aid providers in the recognition of the signs of sepsis and septic shock with many novel tools such as qSOFA scores, a promising step in the right direction. EMS providers should be equipped with diagnostic means that are proven and feasible for use in the field such as ETCO2 and POC lactate monitoring to improve diagnostic accuracy and ability. Finally, providers should initiate supportive therapy such as IVF administration or vasopressor infusions in line with hospital protocols in cases where the patient is in serious enough condition. These changes are simple to implement as they do not require large amounts of additional equipment or burden on ambulance companies but do present a potentially huge improvement in current methods. These changes, coupled with the promise of future improvements such as the advent of community paramedicine, and means of faster recognition and treatment, should be considered as they become viable for use. Hopefully this improved integration of EMS and Hospital care drives down the currently high mortality rates and incidences of sepsis and aids in combating one of the most serious medical conditions our society currently faces.

LIST OF JOURNAL ABBREVIATIONS

Acad Emrg Med	Academic Emergency Medicine
AHRQ	Agency for Healthcare Research
AMIA Annu Symp Proc	American Medical Informatics Association Annual Symposium Proceedings
Am J Emerg Med	American Journal of Emergency Medicine
Am J Resp Crit Care Med	American Journal of Respiratory Critical Care Medicine
Ann Am Thorac Soc	Annals of The American Thoracic Society
Ann Emerg Med	Annals of Emergency Medicine
Ann Transl Med	Annals of Translational Medicine
Antimicrob Agents Chemother	Antimicrobial Agents and Chemotherapy
Biochem Biophys Res Commun	Biochemical and Biophysical Research Communications
BMC Emerg Med	BMC Emergency Medicine
BMJ	The British Medical Journal
Br J Nurs	British Journal of Nursing
Chin Med J	Chinese Medical Journal (English Version)

Clin Infect Dis	Clinical Infectious Disease
Crit Care	Critical Care
Crit Care Med	Critical Care Medicine
Emerg Med Int	Emergency Medicine International
Expert Rev Anti infect Ther	Expert Review of anti-infective Therapy
Front Endocrinol	Frontiers in Endocrinology
Health Aff	Health Affairs
Infect Immun	Infection and Immunity
Intensive Care Med	Intensive Care Medicine
Intensive Care Med Exp	Intensive Care Medicine Experimental
Intern Emerg Med	Internal and Emergency Medicine
Int J Crit Illn Inj Sci	International Journal of Critical Illness and Injury Science
Int J Emerg Med	International Journal of Emergency Medicine
Int J Nurs Stud	International Journal of Nursing Studies
JAMA	The Journal of the American Medical Association
J Cardiovasc Thorac Res	The Journal of Cardiovascular and Thoracic Research

J Clin Invest	Journal of Clinical Investigation
J Crit Care	Journal of Critical Care
J Emerg Med	The Journal of Emergency Medicine
J Emerg Nurs	The Journal of Emergency Nursing
J Immunol	The Journey of Immunology
J Intensive Care	Journal of Intensive Care
J Neurosurg Anesthesiol	Journal of Neurosurgical Anesthiology
J Thoracic Dis	Journal of Thoracic Disease
Lab Invest	Laboratory investigation
Mil Med Res	Military Medical Research
NEJM	The New England Journal of Medicine
NJM	The Netherlands Journal of Medicine
PLOS One	Public Library of Science One
Prehosp Emerg Care	Prehospital Emergency Care
Scand J Trauma Resusc Emerg Med	Scandinavian Journal of Trauma Resuscitation and Emergency Medicine
Singapore Med J	Singapore Medical Journal

Surg Infect	Surgical Infections
Ther Adv Drug Saf	Therapeutic Advances in Drug Safety
Ther Clin Risk Manag	Therapeutics and Clinical Risk Management
West J Emerg Med	Western Journey of Emergency Medicine
World J Crit Care Med	World Journal of Critical Care Medicine Aging Health

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